REMARKS

Claims 1-42 are pending in this application, with claims 11-42 withdrawn as directed towards non-elected subject matter. Claims 1-10 were rejected under 35 U.S.C. §112, second paragraph. Claims 1-10 were rejected under 35 U.S.C. §102(b). Claims 1-10 were rejected under 35 U.S.C. §103(a).

By this Amendment, claims 4-6, 9 and 10 have been cancelled, claim 2 has been amended, and new claims 43-107 have been added, without prejudice or disclaimer of any previously claimed subject matter, leaving claims 1-3, 7, 8, and 43-107 under consideration.

Support for the amendments to the claims may be found at page 23, line 23, through page 24, line 4 and in the language of the originally filed claims. Support for the new claims may be found at page 17, lines 17-19, page 23, lines 12-15, page 36, line 21, through page 38, line 2, page 43, lines 11-26, page 48, line 3, Table 1 and page 71, lines 19-28. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

With respect to any claim amendments or cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Restriction of claims and request for rejoinder

Applicants gratefully acknowledge the Examiner's withdrawal of the restriction between Groups II, III, and IV.

Upon a finding that the product claims under consideration are allowable, Applicants respectfully request rejoinder of withdrawn process claims which include all of the limitations of the allowable product claim for examination. M.P.E.P. § 821.04.

Rejections under 35 U.S.C. § 112

A. Claims 1-10 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner asserts that the phrase "a population" is indefinite because it is unclear whether the claimed population is made up of homogenous or heterogeneous conjugate molecules. Applicants respectfully traverse this ground for rejection.

Applicants respectfully submit that claims 1-10 are not indefinite for use of the term "a population." As is made clear by the specification, Applicants have discovered that conjugates of an immunostimulatory sequence polynucleotide (ISS) and an antigen having different extents of conjugation (*i.e.*, the number of ISS molecules conjugated to each molecule of antigen) have markedly different immunomodulatory activities. Further, Applicants note that the phrase "population of conjugate molecules" is defined at page 14, lines 14-24. The definition, as well as the rest of the specification, makes clear that a given population is heterogeneous:

> For purposes of this invention, it is understood that such populations do not necessarily have, and may or may not have a constant number of ISS attached to each antigen molecule. Typically, a given population will have a distribution of molecular weights (based on varying extent of conjugation within a give population) and thus an average number of ISS conjugated to antigen.

In view of this clear teaching by the specification, Applicants respectfully submit that one of skill in the art would understand that the claimed populations are heterogeneous as to the extent of conjugation, within the limits proscribed by the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Claim 2 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner asserts that it is unclear if the phrase "is greater than about 1000" refers to the extent of conjugation or the amount of histamine released by antigen-stimulated basophils. Applicants respectfully traverse this ground for rejection.

Applicants respectfully submit that the phrase "is greater than about 1000" in claim 2 would be clearly understood by one of ordinary skill in the art to refer to the ratio of the concentration of conjugate to the concentration of allergen. However, in the interest of

expediting prosecution, Applicants have made an non-narrowing amendment which more particularly and distinctly points out that the phrase "is greater than about 1000" refers to the ratio. Accordingly, Applicants respectfully submit that this ground for rejection has been obviated, and respectfully request that it be withdrawn.

C. Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner asserts that it is unclear if the phrase "about 100 to about 200" refers to the extent of conjugation or the amount of histamine released by antigen-stimulated basophils.

Applicants have cancelled claim 5 without prejudice or disclaimer, rendering this rejection moot. Accordingly, Applicants respectfully request that this ground for rejection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-10 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by International Patent Application No. WO 98/16247 ("Carson et al."). The Examiner asserts that claims 1-10 are anticipated by the disclosure of ISS/antigen conjugates made with a 5:1 ratio of ISS to antigen.[1] Applicants respectfully traverse this ground for rejection.

Applicants have cancelled claims 4-6, 9, and 10 without prejudice or disclaimer, rendering this ground for rejection moot as it pertains to those claims. With regard to the remaining claims, Applicants respectfully submit that Carson et al. fails as an anticipatory reference. The figure legends of Carson et al. state that the ISS/antigen conjugates employed are at a 5:1 (ISS:antigen) ratio.[2] In contrast, claims 1 and 2 recite a population of conjugates which are conjugated to an extent that results in: a 50% binding inhibition ratio of about 3.5 to about

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[1] The Examiner refers to "...the concentration of the conjugate to the antigen is 5:1..." Office Action, page 3, section 9. With this ratio, Applicants assume the Examiner means to an ISS to antigen ratio.

[2] Applicants note that all of the figure legends of Carson et al. state that the ratio of ISS:antigen used was 5:1. However, twice the conjugates are referred to as "ISS-PN/IMM (1:5 ratio)" (on page 7, lines 3-4 and line 17) which, based on the rest of the disclosure, is an apparent clerical error.

6.0 (in terms of concentration of ISS-antigen conjugate to concentration of antigen; claim 1, and specification at page 23, lines 16-22) and a 40% histamine release ratio of greater than about 1000 (in terms of concentration of ISS-antigen conjugate to concentration of antigen; claim 2 and specification at page 23, line 23, to page 24, line 4). Carson et al.'s disclosure of conjugates made at a ratio of 5:1 (ISS to antigen) fails to disclose each and every limitation of the instant pending claims, and therefore cannot anticipate the instant pending claims. Further, Carson et al. fails to teach anything with respect to any desirability or effect of greater extents of conjugation. Carson et al.'s only reference to a ratio is by a single working example which describes a single ratio of ISS to antigen,[3] and contains no disclosure regarding variation of the ratio or of the reaction time, let alone even a suggestion of Applicants' discovery regarding the differing effects and/or properties of ISS/antigen conjugates having different extents of ISS:antigen ratios.

New claims 63 and 75 recite a population of conjugates which are conjugated to an extent that results in: an average ratio of ISS-containing polynucleotide to antigen of at least about 5.5 (claim 63, and specification at page 23, lines 12-13) and an average mass ratio of ISS-containing polynucleotide to antigen of at least 45 to 40, or an average mass ratio of at least 1.1 (claim 75, and specification at page 23, lines 14-15). Carson et al.'s disclosure of conjugates made at a ratio of 5:1 (ISS to antigen) fails to disclose each and every limitation of these new claims.

Thus Carson et al. fails to disclose the instant claimed invention. Accordingly, Applicants respectfully submit request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-10 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,225,292, ("the '292 patent) in view of Hirschwehr et al., 1995, *J. Allergy Clin. Immunol.* 101:196-206 ("Hirschwehr et al."). The Examiner asserts that the '292 patent teaches

[3] As noted above, although the figure legends of Carson et al. all state that the ratio of ISS:antigen used was 5:1, twice the conjugates are referred to as "ISS-PN/IMM (1:5 ratio)" (on page 7, lines 3-4 and line 17) which, based on the rest of the disclosure, is an apparent clerical error.

the production of ISS/antigen conjugate molecules, and that Hirschwehr et al. teaches that Amb a1 and mugwort antigens share similar structures. Applicants respectfully traverse this ground for rejection.

Applicants respectfully submit that the instant claimed invention is not obvious over '292 patent in view of Hirschwehr et al. Applicants' invention relates to classes of conjugates comprising immuno*stimulatory* sequence (ISS) containing polynucleotides and antigens, which are based on the extent of conjugation. The extent of conjugation in these populations gives rise to certain properties and/or effects. The '292 patent is directed towards immuno*inhibitory* (IIS) polynucleotides which may be optionally conjugated to an antigen. The '292 patent contains no teach or suggestion regarding conjugates having different extents of conjugation. Accordingly, Applicants respectfully submit that the '292 patent fails to teach or suggest the instant claimed invention. Further, Applicants respectfully point out that the particular structural and/or functional properties are recited in the claimed populations (*e.g.*, "the population is such that the ratio of (i) concentration of ISS-antigen conjugate required for 50% inhibition of binding of antigen-specific antibody to antigen to (ii) concentration of antigen required for 50% inhibition of antigen-specific antibody to antigen is about 3.5 to about 6.0"). The cited reference nowhere teaches or suggests these properties.

Finally, Hirschwehr et al. fails to cure the deficiencies of the '292 patent, as it is limited to the properties of certain allergens, and teaches nothing about conjugation with immunostimulatory polynucleotides, let alone Applicants' discoveries relating to different classes of conjugates.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the claims are now in condition for allowance. Early notification to this effect is earnestly requested. Should Examiner Huynh find any issues outstanding, he is respectfully requested to contact the undersigned at 650-813-5895, or to contact Nick Buffinger, also of record in this application, at 650-813-5816.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001500.

Respectfully submitted,

Dated: May 6, 2002

By: Karen R Zachow

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5859
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

2. (Amended) A population of conjugate molecules, said conjugate molecules ~~comprising an antigen and a polynucleotide comprising an immunostimulatory sequence~~ (ISS), wherein the antigen is an allergen, and wherein the extent of conjugation in the population provides a 40% histamine release ratio of greater than about 500, said ratio calculated as [is such that] the ratio of (i) concentration of ISS-antigen conjugate required for about 40% histamine release from basophils from an antigen-sensitized individual to (ii) concentration of antigen required for about 40% histamine release from basophils from an antigen-sensitized individual [is greater than about 1000].